U.S. EPA High Production Volume (HPV) Chemical Challenge Program

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SUMMARY OF EXISTING DATA, PROPOSED TEST PLAN AND RATIONALE FOR CALCIUM DIPROPIONATE (CASRN 4075-81-4)

Prepared by

MorningStar Consulting, Inc.

on behalf of

OM Group, Inc.

The Sponsoring Company

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INTRODUCTION

The following document includes a test plan and a summary of existing data for calcium salt of propionic acid (Ca dipropionate) [CASRN 4075-81-4]. The information provided in this document and the attached dossier of robust summaries meets the requirements under the U.S. High Production Volume (HPV) Chemical Challenge. Ca dipropionate is one of 19 sponsored chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. Ca dipropionate is sponsored by the OM Group (OMG).

USE PATTERNS AND REGULATORY BACKGROUND

Ca dipropionate, [$2(CH_3CH_2COOH^-)$ Ca^{2+}] is a metal carboxylic acid, a salt of calcium and the alpha monocarboxylic acid, propionic acid. Ca dipropionate is used in variety of ways including as a common food and feed additive, as a pesticide active ingredient (fungicide), and as an inert ingredient in pesticides. Since 1979 the Code of Federal Regulations (CFR) has listed Ca dipropionate (21 CFR 182.3221), propionic acid [21 CFR 182.3081] and the sodium salt, Na propionate [21 CFR 182.3784] as a generally recognized as safe (GRAS) chemical preservative in food (FASEB 1979). Products such as these are commonly used as additives in cheese and milk products, meats, beverages and other consumer products.

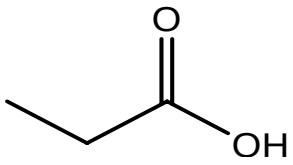
The EPA Office of Pesticide Programs (OPP) recently released a Final Rule exempting from tolerance the residues of these three chemicals in raw agricultural commodities pursuant to section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA). The tolerance for propionic acid (also known as propanoic acid)[1] is found in 40 CFR Part 180 and was announced in the Federal Register August 4, 2004 (Vol. 69, No. 149). Under this exemption, Ca dipropionate residues are permitted to be present in, or added to, any agricultural product with no restriction on the amount of residue present. This tolerance exemption provides a recent affirmation of the status of Ca dipropionate and propionic acid as GRAS. An excerpt of the August 4 *Federal Register* explains:

> *Based on "…the low potential for toxicity of propanoic acid [a synonym for propionic acid] and its calcium and sodium salts for the oral route of exposure, that humans of all ages are highly exposed to propanoic acid from natural sources, and that the human body has a known pathway for metabolizing propanoic acid…EPA concludes that exempting propanoic acid, and its calcium and sodium salts from the requirements of a tolerance will be safe for*

the public, including infants and children" (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).

These same compounds have also been evaluated internationally. The safety of these compounds for use in food has been evaluated several times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Propionic acid and three of its simple salts (Ca^{2+}, Na^{+}, K^{+}) have been established internationally as common food additives used as mold inhibitors, preservatives, and flavoring agents. The JECFA concluded as recently as 1997 that there is no safety concern for these compounds at the current levels of use and that their Acceptable Daily Intake (ADI) need not be limited. Propionates are metabolized and utilized in the same way as a normal fatty acid (JECFA, 1962). The toxicology evaluation for these compounds concluded that there is no reason to believe that the propionic acid differs toxicologically from its calcium and sodium salts (JECFA, 1966).

Figure 1: Structures of Ca dipropionate



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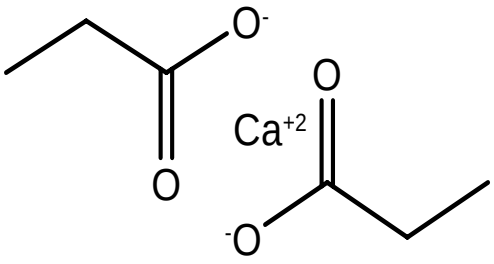

B

A) Propionate (as the free acid)

B) Ca dipropionate

Ca dipropionate is considered a "simple" salt due to the presence of calcium. This divalent metal action is not considered toxicologically significant. Calcium is an essential element that is absorbed mainly through active transport. The amount absorbed is regulated according to the current needs of the body with the participation of vitamin D, parathormone, and calcitonin. Normal calcium absorption requires the presence of vitamin D, a Ca-binding protein and amino acid (lysine and L-arginine).

One characteristic of Ca dipropionate and other metal carboxylates is that they are ion pairs, which readily dissociate in water. The dissociation constants show that at the low pH of the stomach, the important moieties from a toxicological standpoint are the unionized free acid and ionized metal. Because of this, mammalian toxicity data for the free acid, or that for a simple salt of the acid (e.g., the sodium salt or the calcium salt), can serve as surrogate data for the acid component of respective metal carboxylates such as Ca dipropionate. Table 1 shows how similar the acute toxicity data is for the salt, Ca dipropionate, and

the free acid, propionate. Under these conditions, the contribution of the metal ion (Ca^{+2}) to any observed toxicity is considered minimal or insignificant. This is supported by the treatment of the acid and the Ca and Na salts as equivalent in the recent Exemption of Tolerance decision by the EPA (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).

Table 1. Comparison of acute toxicity values for Ca dipropionate and its carboxylic acid, propionate

Acute Mammalian Toxicity[a]	**Ca dipropionate**	**Propionate**
Acute oral toxicity (LD50 in mg/kg bw)	3920-4380	2600-4290
Acute inhalation toxicity (LC50 in mg/L)	>5.4	>4.9
Acute dermal toxicity (LD50 in mg/kg bw)	500	500

[a] See Table I

For this reason the data for the free acid, propionate, are clearly delineated as supporting data and summarized and referenced in the appropriate "Remarks" sections for each data element in the robust summaries of Ca dipropionate. These data are also presented in Tables I.

EXISTING DATA FOR CA DIPROPIONATE – SUMMARY

Physicochemical Properties

Available physicochemical property data for this compound and its carboxylic acid are shown in Table I and briefly summarized below.

Physicochemical properties are well characterized for Ca dipropionate. Data for all five physicochemical endpoints are available for either Ca dipropionate or propionic acid (Table I) (IUCLID 2000b).

Melting Point

The melting point was not applicable (NA) for the Ca salt, but was reported as 22.4^{o}C for the acid.

Boiling Point

Boiling point was evaluated in a GLP study in 2004, but could not be measured under the test conditions (RCC 2003). The reported values for the boiling point of propionic acid are 140.7 to 141.6^{o}C (IUCLID 2000b).

Density

Density for Ca dipropionate is reported as 400 mg/m^3 (IUCLID 2000a)

Vapor Pressure

Vapor pressure was not considered applicable for Ca dipropionate, but was reported as 5 hPa at 20^{o}C for the acid (IUCLID 2000b).

Partition Coefficient

The Log octanol/water partition coefficient for the acid was reported to be very low at 0.25-0.33, but was not evaluated for the Ca dipropionate salt, which is not a pure substance (IUCLID 2000b).

Water Solubility

Ca dipropionate was reported to have a substantial solubility of 260g/L at 20^{o}C (IUCLID 2000a) and the acid has a reported water solubility of 55.8 g/100ml @100^{o}C (HSDB 2002).

Environmental Fate and Transport

Available environmental fate and transport data for Ca dipropionate and propionic acid are shown in Table I and summarized below.

Photolysis

Photolysis was not measured for Ca dipropionate, but was measured for the free acid. The rate of degradation was 1.22-1.60 E^{-12} CM^3/mole/s @298^oK (Adkinson 1993).

Dissociation in water

One key characteristic of any metal carboxylate is that they readily dissociate from an ion pair into free metal and free acid as the pH is decreased. The equilibrium constants from a recent GLP dissociation study with Ca dipropionate can be seen in Table 2 (below), and the pKb values for propionate from the scientific literature are very consistent with the measured pKb2 value from the dissociation study (see bolded values).

Table 2 Comparison of pK values for Ca dipropionate, the metal carboxylate salt, and respective carboxylic acid[a]

Chemical Tested	Equilibrium Constants	
	pKb1	pKb2
Propionate	**4.87**	
Ca dipropionate	6.67	**4.75**

[a] See Table I and the Robust Summaries for additional details.

Biodegradation

The calcium salt of propionic acid is readily biodegradable and, as is the case for the acid, does not persist for long periods in water. The salt is 100% degraded after 7 days (Lezotte 2003) and the acid shows a similar rate of degradation of 95% in 10 days (IUCLID 2000b).

Monitoring data

Residues in foods, measured as propionic acid range from approximately 1100 to 2000 ppm (IUCLID 2000b, FASEB 1979).

Transport data

The Fugacity Level III analysis (Episuite v. 3.20) has been run for the Ca dipropionate (salt) and for the propionic acid dissociation product. This data is provided in the robust summaries. The propionic acid data is included in the

remarks section of 3.3.1 Transport (Fugacity). This modeling is not appropriate for either the salt or the acid due to the presence of the metal and ionized nature of the acid and the results must be carefully interpreted. The model is designed for neutral organics.

For the Ca dipropionate salt the fugacity calculations are performed assuming equal inputs to each compartment (air, water soil and sediment). Input parameters are generated within the Episuite program. Results show that the mass amount in each of four compartments partitions most strongly to soil and then water with only minor amounts in air and sediments (see Table below). Half-lives in these compartments are short ranging from 281 to 720 hr. with a longer half-life in sediment.

Ca dipropionate

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0336	281	1000
Water	38.8	360	1000
Soil	61.1	720	1000
Sediment	0.0713	3.24e+003	0

Fugacity III modeling with acid propionate was specifically requested by the EPA and is presented under the remarks section for section 3.3.1 of the robust summary. The results are very similar to the salt with similar mass amounts in each compartment. The exception is the acid in the air compartment which has a larger mass amount than the Ca salt. The half-lives are shorter in three compartments and similar in sediments relative to Ca propionate. Half-lives range from 210 to 416 hr. for air water and soil. Sediments are slower, but have very little mass of propionic acid present.

Propionic acid

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.12	210	1000
Water	37.5	208	1000
Soil	56.3	416	1000
Sediment	0.0662	1.87e+003	0

Half-lives are short (<30 days) for air, water and soil for both Ca dipropionate and shorter (<18 days) for propionic acid indicating these materials would not result in any environmental persistence.

Ecotoxicity

Fish Toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with the reported 96-h LC50 value for *Leuciscus idus* reported as >10,000 mg/L (Table I) (BASF AG 1990). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for salmon and trout, respectively (IUCLID 2000b).

Invertebrate toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with reported 48-h LC50 value of > 500 mg/L (Table I) for *Daphnia* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for *Daphnia sp*., respectively (IUCLID 2000b).

Algal toxicity

The calcium salt of propionic acid is practically non-toxic toward algal species with reported 96-h IC50 value of > 500 mg/L (Table I) for *Scenedesmus subspecatus* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 43.0 to 45.8 mg/L for *Scenedesmus subspecatus* (IUCLID 2000b).

Propionic acid is slightly toxicity to fish, invertebrates and algae with LC50 values ranging from 22.7 to 85.3 mg/L. The higher toxicity of the acid appears to be mainly due to the effects of low pH, as toxicity is greatly reduced under neutralized conditions.

Human Health Effects

Propionic acid is a normal intermediary metabolite in animals and humans. There is an extensive mammalian toxicity database available for this compound and the salt, Ca dipropionate.

Acute Mammalian Toxicity

Acute toxicity data is available Ca dipropionate for five of five acute endpoints (i.e., oral toxicity, inhalation, dermal toxicity, skin irritation and eye irritation) and two endpoints for the acid as presented and referenced in Table I (Kobayashi et al. 1976, BASF AG 1980, Patty Ind. Hyg. Toxicol. 1982, Symth et al. 1962, BASF AG 1979). Ca dipropionate shows a low order of acute toxicity and no irritation. The same order of toxicity is reported for propionate.

The acid has a low acute toxicity in animal studies (Table I), and is not reported to be corrosive or irritating to skin and eyes. Oral, inhalation and dermal LD50 or LC50 values are 3920-4380 mg/kg (rat), >5.6 mg/L (4 hrs., rat), and 500 mg/kg bw (rabbit). Reported acute toxicity in the rat exposed to propionic acid range from 2600 to 4290 mg/kg and >4.9 mg/L (4 hrs.) for oral and inhalation routes, respectively (IUCLID 2000b). Ca dipropionate is reported to be "not irritating", to either the skin or eye in rabbits using the Draize test (BASF AG 1979).

Genetic Toxicology - Mutation Assays

Neither Ca dipropionate nor propionic acid is mutagenic in *in vitro* Ames Tests. Genetic Toxicity Studies are available for Ca dipropionate and the carboxylic acid, propionate. *In vitro* Ames bacterial assays have been used to evaluate Ca dipropionate, including at least 11 strains with and without activation and with standard strains (e.g., TA 98, TA100, TA1535, TA1537, and TA1538) being evaluated in multiple studies (Altman et al. 1988a, Ohta et al. 1980, Litton Bionetics, Inc. 1974, Ishidata et al. 1984). All studies were negative for mutagenicity of Ca dipropionate. Similar *in vitro* studies with propionic acid and Na propionate were all negative. Similar results were observed in an *in vitro* study with Chinese hamster lung cells (without activation) and in sister chromatid exchange assays, using V79 cells (with and without activation) (Basler et al. 1987).

Genetic Toxicology – Clastogenic

Ca dipropionate is negative in cytogenetic or dominant lethal assays (Table I). Propionic acid is negative in a micronucleus test. In *in vivo* studies, Ca dipropionate showed no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutations were observed (Litton Bionetics 1974). In the mouse exposure to Ca dipropionate resulted in increased reversion frequency, in one of three strains, but this was not dose-related. Propionic acid is reported to be negative in a micronucleus test (Basler et al. 1987).

In summary, all genetic toxicity studies using bacterial and mammalian cells, *in vitro* or *in vivo* are consistently negative.

Repeated Dose

There is extensive toxicity data for Ca dipropionate including several long-term repeated dose studies. This salt has a low order toxicity and it is typically less toxic that the acid alone, likely due to its lower acidity.

Repeated dose studies were conducted in rats and dogs with study periods ranging from 4 weeks to 90 days and exposure levels ranging up to 3320 mg/kg/day. No abnormalities in clinical or hematological examinations were observed. These changes were largely reversible. Changes in the fore stomach (e.g., hyperkeritosis and hyperplasia) were observed. These

changes were observed to occur equally with Ca and Na propionate, but were more marked with exposure to propionic acid. The changes were largely reversible, attributed to the acidity of the compound, and were not related to any systemic toxicity of the compound. Studies with Na propionate and propionic acid are also available. Some of these were conducted in parallel with Ca dipropionate (Altman et al. 1988a, Altman et al. 1988b, Harshbarger 1942).

Developmental Studies

Developmental studies have been conducted with five species (mouse, rabbit, hamster, rat, and chicken) (Food and Drug Research Labs Inc. 1972, Miss. State Univ. 1973). All five studies are rated as "Reliable with Restriction". In the four studies with mammalian species, no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls. Parameters monitored including food and water consumption; body weight during early gestation; numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses; body weights of live pups; dam urogenital tract examination; examination of all fetuses for gross abnormalities and one third for visceral abnormalities; and one third of fetuses were preserved, stained and examined for skeletal defects. In the study with chickens, Ca dipropionate was not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg pre-incubation or at 96 hours via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered pre-incubation via the yolk caused a high mortality rate (FASEB 1979).

Reproduction Studies

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure to propionate, no reproduction data is recommended.

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Table I: Summary of existing data for Ca dipropionate and its carboxylic acid

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate[a]
Physicochemical Properties			
Melting Point		NA[1]	22.4°C
Boiling Point		….[b]	140.7–141.6 °C
Density		400 mg/m^3 [c]	
Vapor pressure		NA	5 hPa at 20 °C
Log Partition Coefficient		….[2]	0.25-0.33
Water Solubility		260 g/L at 20°C[c]--	49 g/100 ml at 0°C; 55.8 g/100 ml at 100°C[d]
Environmental Fate Parameters			
Photodegradation		--	1.22-1.60 E^{-12} cm^3/mol/s at 298°K[e]
Dissociation in water		pKb 6.7 and 4.75 at 20°C[f]	pKb 4.78
Monitoring Data	Food[3]		Ca 1100 to 2000 ppm[c,g]
Transport	NA[c]	See robust summary	See robust summary
Biodegradation		100% degraded after 7 days [h]	40% removal after 24 hrs. and 95% removal after 10 days.
Ecotoxicity			
Fish toxicity (96-h)	Bluegill Trout	>10,000 mg/L[i] (*Leuciscus idus)*	96-h LC50 for trout and salmon are 85.3 and 67.1 mg/L respectively
Invertebrate toxicity (48-h)	*Daphnia*	> 500 mg/L in (*Daphnia)*[j]	Ranged from 22.7 to 50 mg/L (*Daphnia)*
Algae toxicity (96-h)		>500 mg/L (Scenedesmus subspicatus)[j]	43 to 45.8 mg/L (Scenedesmus subspicatus)
Human Health Effects			
Acute	Oral LD50, rat	3920-4380 mg/kg bw[k]	3470, 4290, and 2600 mg/kg bw
	Inhalation LC50, rat	>5.6 mg/L (4 hrs.)[l]	>4.9 mg/L (4 hrs.)
	Dermal LD50, rabbit	500 mg/kg bw[m,n]	---
	Skin irritation, rabbit	Not irritating in Draize Test[o]	---
	Eye irritation	Not irritating[o]	---

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate
Repeated dose	90-day oral	Reversible changes in stomach mucosa, but no mortality, no abnormalities following clinical and hematological examination and no change in organ weights were observed following exposures up to 3320 mg/kg/day[pqr]	pH related lesions in mucosal wall following 21 to 28 day exposures at 3320 mg/kg/day
Genetic Toxicology – mutation assay	Ames bacterial reversion assay	Negative[p,s,t,u]	Negative[v]
Genetic Toxicology – Clastogenic	Cytogenetic and dominant lethal assay	Negative (No increased chromosomal aberrations in bone marrow cells)[t]	Negative (micronucleus test)[v]
Reproductive		NA	NA
Developmental		No teratogenic effects in five species tested[x,y]	NA

[a] IUCLID 2000b; [b] RCC 2003; [c] IUCLID. 2000a; [d] HSDB. 2002; [e] Adkinson. 1993; [f] Lezotte 2003; [g] FASEB 1979; [h] BASF AG 1989b; [i] BASF AG 1990; [j] BASF AG 1988; [k] Kobayashi et al. 1976; [l] BASF AG 1980; [m] Patty Ind. Hyg. Toxicol. 1982; n Symth et al. 1962; [o] BASF AG 1979; [p] Altman et al. 1988a, [q] Altman et al. 1988b; [r] Harshbarger 1942; [s] Ohta et al. 1980; [t] Litton Bionetics, Inc. 1974; [u] Ishidata et al. 1984; [v] Basler et al. 1987; [x] Food and Drug Research Labs 1972; [y] Mississippi State University (1973).

1. Boiling Point could not be measured under conditions of GLP Test

2 The octanol/water partition coefficient was not measured for any of the metal carboxylates because they are salts which dissociate into ionized substances and they are not pure substances.

3 Estimated levels reported to be found in baked goods.

TEST PLAN AND RATIONALE FOR CA DIPROPIONATE

Propionic Acid, Calcium Salt	CASRN 4075-81-4

The Test Plan for Ca dipropionate is presented in Table II with supporting data for the carboxylic acid, propionate. The rationale for the Test Plan is based upon existing data as summarized above and in Table I. Some data is older, but this entire dataset has consistently served as an adequate basis for addressing food safety concerns by FDA, WHO, and most recently by the EPA (Office of Pesticide Programs). Furthermore, key studies have a rating of [1] reliable without restriction or [2] reliable with restrictions.

Physicochemical Properties

Data is available for all five SIDS endpoints listed in Tables I and II for either Ca dipropionate or propionic acid. The melting point and vapor pressure studies were considered not applicable and data was available for the free acid. A GLP boiling point study (OECD 103) was conducted, but the BP could not be determined under the conditions of the test (RCC 2003). The rationale for not conducting an octanol/water partition coefficient study with Ca dipropionate is based on the impurity of the compound (i.e. a salt), and an ionizeable substance. Using a compound with these characteristics to measure the partition coefficient is inappropriate. This would yield erroneous data. Data is available for the acid, which shows the Log Kow to be very low. No additional testing is recommended for any of the physicochemical endpoints.

Environmental Fate Parameters

Adequate data is available for three SIDS endpoints (i.e., photodegradation, dissociation and biodegradation) for Ca dipropionate and/or propionic acid. Data for transport in the environment is not provided and is not considered necessary. Standard models used for estimating transport do not accurately predict salts or ionized substances. Adequate biodegradation data are currently available for propionic acid component of the salt. The acid rapidly biodegrades (IUCLID 2000b). Further, aerobic degradation data already exists for Ca dipropionate and shows that it rapidly biodegrades. Because propionic acid is known to occur naturally and to readily be metabolized and degraded *in vivo,* and in the environment, estimating the environmental transport is considered unnecessary.

Ecotoxicity

Sufficient data is available for Ca dipropionate and for the carboxylic acid, propionic acid, for all three types of organisms (i.e., fish, invertebrates and algae). Based on the low order of toxicity for both the Ca salt and the acid for all three endpoints no additional studies are recommended.

Human Health Effects

Acute toxicity studies

Acute oral toxicity data is available for the Ca dipropionate and dissociation product propionic acid for five acute toxicity endpoints (oral toxicity, inhalation, dermal toxicity and skin and eye irritation) (Table I). No additional studies are recommended for acute toxicity endpoints.

Genotoxicity studies

Existing data for Ca dipropionate and the carboxylic acid, propionate are all negative (Table I). No additional genetic toxicity studies are proposed.

Higher tiered studies

Numerous repeated dose studies with Ca dipropionate, Na propionate, and the free acid, propionate, show a consistent lack of effects with the exception of changes in the digestive tract mucosa. These changes are largely reversible and attributed to generic pH effects and not to systemic toxicity. No additional repeated dose studies are recommended.

Developmental studies were conducted with four mammalian species and consistently showed a lack of teratogenic effects. There were no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival. A study with chickens also showed a lack of teratogenicity. These studies were conducted in the early 1970's by the Food and Drug Research Labs and Litton Bionetics prior to the establishment of guidelines. They are rated as [2] Reliable with Restrictions. No additional studies are recommended.

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure of organisms to propionate via diet, no additional testing is recommended.

Table II: Test Plan Matrix: Ca dipropionate

	Information available	Ca Dipropionate	Propionate	GLP Study	Acceptable	Testing recommended
PHYSICOCHEMICAL PROPERTIES						
Melting Point	Y	Y	N	Y	Y	N
Boiling Point	Y	Y	Y	Y	Y	N
Vapor pressure	Y	N	Y	N	Y	N
Partition Coefficient	Y	N	Y	Y	Y	N
Water Solubility	Y	Y	N	N	N	N
ENVIRONMENTAL FATE PARAMETERS						
Photodegradation	Y	N	Y	--[C]	--	N
Dissociation in water	Y	Y	N	Y	Y	N
Transport	Y	Y	Y	N	Y	N
Biodegradation	Y	Y	Y	--	Y	N
ECOTOXICITY						
Fish toxicity (96-h)	Y	Y	Y	Y	Y	N
Invertebrate toxicity (48-h	Y	Y	Y	Y	Y	N
Algae toxicity (72-h)	Y	Y	Y	--	N	N
HUMAN HEALTH EFFECTS						
Acute						
Oral LD50, rat	Y	Y	Y	N	Y	N
Inhalation LC50, rat	Y	Y	Y	N	Y	N
Dermal LD50, rat	Y	Y	N	N	Y	N
Skin Irritation	Y	Y	N	N	Y	N
Eye Irritation	Y	Y	N	N	Y	N
Repeated dose	Y	Y	Y	Y	Y	N
Genetic Toxicology – mutation assay	Y	Y	Y	Y	Y	N
Genetic Toxicology – chromosomal aberration	Y	Y	Y	Y	Y	N
Reproductive	N	N	N	N	Y	N
Developmental	Y	Y	N	Y	Y	N

[A] U = undetermined
[B] Study currently being conducted
[c] -- means not applicable

201-16574C

Note: Appendix I refers to the IUCLID profile for Propionic acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Propionic acid, calcium salt
Chemical Name	:	Propionic acid, calcium salt
CAS Registry No.	:	4075-81-4
Component Cas Nos.	:	
EINECS No.	:	223-795-8
Structural Formula	:	$C_6H_{10}CaO_4$
Molecular Weight	:	186.2226
Synonyms and Tradenames	:	Calcium dipropionate; calcium propionate; calcium propanoate; propanoic acid, calcium salt; Bioban-C; Luprosil Spezial; Mycoban
Reference	:	http://www.chemfinder.com; MSDS dated 6/6/01 prepared by Kemin Industries, Ltd.; MSDS as cited in IUCLID (2000). IUCLID Dataset. European Chemicals Bureau, European Commission. Dataset for Calcium Dipropionate, 2/18/2000. [Subsequently referenced as IUCLID (2000)]

2.1 MELTING POINT

Type	:	
Guideline/method	:	OECD 103
Value	:	Could not be determined under the test conditions
Decomposition	:	
Sublimation	:	
Year	:	2003
GLP	:	yes
Test substance	:	Propionic acid, calcium salt
Method	:	Thermal Analysis and Capillary Test
Method detail	:	Thermal analysis was conducted using a Differential Scanning Calorimeter using a range of 25°C to 400°C with a change of 20 K/min. The capillary test was conducted using a Buechi Melting Point Tester, B-545. Samples were heated over a range of 25°C to 400°C
Remark	:	**Supporting data for dissocation products:** **Acid:** Melting point for propionic acid is reported to be 22.4°C (See Appendix I: 2.1)
Result	:	During Thermal Analysis endothermic peaks were observed starting at 90°C, a second, small peak at 260°C, and third peak at 360°C the remaining brown residue at the end of the study was half melted. In the Capillary Test the material was unchanged up to 360°C, but above 360°C the material began to sweat and at about 390°C the material started to melt and the color changed to a brown-grey.
Reliability	:	[1] Recent GLP Guideline Study
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable.
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	**Supporting data for dissocation products:** **Acid:** Boiling point for propionic acid is reported to be 140.7 – 141.6°C (See Appendix I: 2.2)
Remark	:	
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.3 DENSITY

Type	:	Bulk density
Guideline/method	:	
Value	:	ca. 400 kg/m^3 at °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	

Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Density for propionic acid is reported to be 0.992 g/cm^3 at 20°C (See Appendix I: 2.3)
Reliability	:	[4] Not assignable. Only secondary reference
Reference	:	MSDS as cited in IUCLID (2000)

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	Not applicable
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Vapor pressure for propionic acid reported to be 5 hPa at 20°C (See Appendix I: 2.4)
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Log Pow for propionic acid reported to be 0.25 – 0.33 (See Appendix I: 2.5)
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method		
Value	:	260 g/L at 20°C
pH value	:	9.2
concentration	:	200 g/L at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at °C
Description	:	

Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Other reported values: 49 g/100 mL at 0°C; 55.8 g/100 mL at 100°C (Hazardous Substances Data Bank, online at http://toxnet.nlm.nih.gov;) [Subequently referred to as HSDB, 2002]
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	MSDS as cited in IUCLID (2000)

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Flash point for propionic acid reported to be 52.3°C (See Appendix I: 2.7)
Reliability	:	
Reference	:	MSDS, Fisher Scientific (2002) from http://www.fishersci.ca/msds/nsf

3.1.1 PHOTODEGRADATION

Type	:	
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	1.22 - 1.60 E-12 cm^3/mol/s at 298ºK (measured for free acid)
Remark	:	**Supporting data for dissocation products:** **Acid:** The calculated time to 50% degradation by indirect photolysis of propionic acid was 4.7 years at room temperature and a pH of 9 with a rate constant of 0.47 x 10^9 L/mol.sec (See Appendix I: 3.1.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Atkinson, R., J. Phys. Chem. RefData, Mongraph 1; Meylan, W. and P. Howard, 1993, Atmospheric Oxidation Program Ver. 1.5, Syracuse Research Corp., NY; As cited in IUCLID (2000)

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	6.76 and 4.75 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Calcium propionate (3445-1), lot number 05322JU, received from Aldrich Chemical Company. White powder, purity of 21.2% calcium
Approximate water solubility	:	Greater than 10,000 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water

Method detail	:	Three replicate samples of calcium propionate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.186 grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 4 incremental additions were made before the first equivalence point and at least 10 incremental additions were made before the second equivalence point. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 4 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKb values were 6.76 (SD = 0.0488) and 4.75 (SD= 0.00808) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of proprionic acid, calcium salt, Wildlife International, Ltd. Study No. 534C-120, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	Food
Concentration	:	ca. 2000 mg/l
Substance measured	:	
Method	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Propionic acid, calcium salt is widely used as a mold and rope inhibitor in bread and bakery products at levels approx. 2000 ppm. Also used to prevent mold in certain cheeses and on certain fruit and vegetable products. (IUCLID, 2000). Weighted mean concentration added to baked goods 1100 ppm (FASEB, 1979)
Reliability	:	[1] Reliable without restriction
Reference	:	IUCLID (2000); Federation of American Societies for Experimental Biology (FASEB), Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients, Report of Select Committee on GRAS substances, prepared for US Food and Drug Administration, 1979. PB80104599 [Subequently referred to as FASEB, 1979]

Additional information: According to the Joint FAO/WHO Expert Committee on Food Additives, the estimate of the acceptable daily intakes for man are given as 0 – 10 mg/kg body weight (unconditional acceptance) and 10 – 20 mg/kg body weight (conditional acceptance). This is calculated as the sum of propionic acid, calcium propionate and sodium propionate. The Expert Commitee stated that there is no reason to believe that propionic acid differs toxicologically from its calcium and sodium salts. (FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases.)

3.3.1 TRANSPORT (Fugacity)

Type	:	

Media : Air – sediment(s) – soil - water
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method : EPISuite, v. 3.20
Method detail : Fugacity calculations performed assuming equal inputs to air, water and soil. Input parameters for physical/chemical properties calculated within EPISuite.
Result : Level III Fugacity Model (Full-Output):

==========

Chem Name : CALCIUM PROPIONATE
Molecular Wt: 186.22
Henry's LC : 1.43e-009 atm-m3/mole (calc VP/Wsol)
Vapor Press : 0.000652 mm Hg (Mpbpwin program)
Liquid VP : 0.00123 mm Hg (super-cooled)
Melting Pt : 53 deg C (Mpbpwin program)
Log Kow : -0.4 (Kowwin program)
Soil Koc : 0.163 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0336	281	1000
Water	38.8	360	1000
Soil	61.1	720	1000
Sediment	0.0713	3.24e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	7.65e-013	1.44	5.83	0.0479	0.194
Water	2.59e-014	1.3e+003	674	43.3	22.5
Soil	1.49e-012	1.02e+003	0	34	0
Sediment	2.37e-014	0.265	0.0248	0.00882	0.000825

Persistence Time: 579 hr
Reaction Time: 748 hr
Advection Time: 2.55e+003 hr
Percent Reacted: 77.3
Percent Advected: 22.7

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 281
Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 2.788 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Note: results were unchanged when water solubility input was changed

from default to the reported value of 260 g/L.

Remark : **Supporting data for dissociation products:**
Acid: For propionic acid,

Fugacity Level III modeling for propionic acid.

Air – sediment(s) – soil - water
% (Fugacity Model Level I)
% (Fugacity Model Level I)
% (Fugacity Model Level I)
% (Fugacity Model Level II/III)
% (Fugacity Model Level II/III)

EPISuite, v. 3.20
Fugacity calculations performed assuming equal inputs to air, water and soil. Input parameters for physical/chemical properties calculated within EPISuite.

Level III Fugacity Model (Full-Output):
==========

Chem Name : Propanoic acid
Molecular Wt: 74.08
Henry's LC : 4.45e-007 atm-m3/mole (Henry database)
Vapor Press : 6.04 mm Hg (Mpbpwin program)
Log Kow : 0.33 (Kowwin program)
Soil Koc : 0.877 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.12	210	1000
Water	37.5	208	1000
Soil	56.3	416	1000
Sediment	0.0662	1.87e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.79e-010	179	544	5.97	18.1
Water	1e-011	1.11e+003	334	37	11.1
Soil	5.19e-010	832	0	27.7	0
Sediment	8.65e-012	0.218	0.0118	0.00726	0.000392

Persistence Time: 296 hr
Reaction Time: 419 hr
Advection Time: 1.01e+003 hr
Percent Reacted: 70.7
Percent Advected: 29.3

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 210.4
Water: 208.1
Soil: 416.2
Sediment: 1873
Biowin estimate: 3.400 (days-weeks)

Reliability : (1) valid with restrictions; calculated using scientifically acceptable method,

		although the applicability of the Fugacity model to test substances such as carboxylic acids is uncertain.
Reference	:	

3.5 BIODEGRADATION

Type	:	Aerobic
Guideline/method	:	OECD 302 B
Inoculum	:	Other: activated sludge
Concentration	:	300 mg/L related to DOC (dissolved organic carbon)
Contact time	:	
Degradation	:	100 % after 7 day(s)
Result	:	
Kinetic of test subst.	:	3 hours = 18 % (specify time and % degradation)
Control substance	:	
Kinetic	:	%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	OECD Guideline 302B, Inherent biodegradability: Modified Zahn-Wellens Test
Method Detail	:	
Result	:	biodegradable
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid is biodegradable in activated sludge, with 40.4% removal of an initial concentration of 500 mg/L after 24 hours and 95% removal of an intial concentration of 400 mg/L after 10 days (See Appendix I: 3.5)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (Ber. V.24.01.89. As cited in IUCLID (2000)

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	Static
Guideline/method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Species	:	*Leuciscus idus*, freshwater fish
Exposure period	:	96 hours
NOEC	:	5000 mg/L
LC0	:	5000 mg/L
LC50	:	> 10000 mg/L
LC100	:	> 10000 mg/L
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1982
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Method detail	:	
Result	:	Lethality to 2 of 10 fish after 96 hours at 10000 mg/L, no lethality at 5000 mg/L. No toxic symptoms detectable.
Remark	:	For sodium propionate, the 24-h LC50 for *Lepomis macrochirus* was 5000 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h LC50 for *Cyprinus carpio* was 72 mg/L and the 24-h LC50 for *Lepomis macrochirus* was 188 mg/L. (See Appendix I: 4.1) Reported 96-h LC50 values for propionic acid include 85.3 ppm (95% CI 73.0 – 99.7ppm) for *Lepomis macrochirus* and 67.1 ppm (95% CI: 61.6 – 73.2 ppm) for *Oncorhynchus mykiss*. (US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 10F0958/885187, 08.01.1990. As cited in IUCLID (2000)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Species	:	*Daphnia magna* (water flea)
Exposure period	:	48 hours
NOEC	:	
EC0	:	250 mg/L
EC50	:	> 500 mg/L
EC100	:	> 500 mg/L
Other	:	24 h EC50 = 250 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1989
GLP	:	No
Test substance	:	Calcium dipropionate

Method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h EC50 for *Daphnia magna* was reported to be 50 mg/L. (See Appendix I: 4.2). Reported 48-h EC50 value for *Daphnia magna* for propionic acid was 22.7 ppm (95% CI: 21.0 – 24.6 ppm) [US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX].
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

4.3 TOXICITY TO AQUATIC PLANTS (e.g., Algae)

Type	:	Growth inhibition
Guideline/method	:	OECD guideline 201, Algae, Growth Inhibition Test
Species	:	*Scenedesmus subspicatus* (freshwater green algae)
Endpoint	:	
Exposure period	:	72 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	> 500 mg/L
EC20	:	> 500 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1988
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	OECD guideline 201, Algae, Growth Inhibition Test
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 72-h EC50 for *Scenedesmus subspicatus* was reported to be 43 - 45.8 mg/L (See Appendix I: 4.3)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behavior	:	
Deg. product	:	
Deg products CAS#		
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid is a normal intermediary metabolite in animals and humans. Propionic acid occurs naturally in various foods including butter and cheese. (FASEB, 1979).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Guideline/method	:	
Species	:	Rat
Strain	:	
Sex	:	Male and female
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	3920 – 4380 mg/kg bw.
Year	:	
GLP	:	
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	
Result	:	LD50 was 3920 – 4380 mg/kg bw. For male rats, LD50 was 4280 or 4380 mg/kg. For female rats, LD50 was 3920 or 4040 mg/kg

Remark	:	For sodium propionate, the LD50 for the rat was 5100 mg/kg. **Supporting data for dissociation products:** **Acid:** For propionic acid, the following LC50 values for rats have been reported: 3470 mg/kg; 4290 mg/kg; 2600 mg/kg. For sodium propionate, the LD50 for the rat was 5100 mg/kg. (See Appendix I: 5.1.1)
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references	:	Other oral LD50 values for rats: 5160 mg/kg bw; 2600 mg/kg bw; 6400 mg/kg bw (As cited in IUCLID, 2000)

Type	:	LD50
Guideline/method	:	
Species	:	Mouse
Strain	:	
Sex	:	Male and female
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	2350 - 2900 mg/kg bw.
Year	:	
GLP	:	
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	
Result	:	LD50 was 2350 - 2900 mg/kg bw. For male mice, LD50 was 2350 or 2600 mg/kg. For female mice, LD50 was 2400 or 2900 mg/kg
Remark	:	For a similar compound, sodium propionate, the LD50 for the mouse was 5100 mg/kg bw, as cited in FASEB Report: Evaluation of the health aspects of propionic acid..., prepared for FDA, 1979.
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references		LD50 of 3340 mg/kg for DD-strain mice is cited in FASEB (1979)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit test
Guideline/method	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hours
LC50	:	> 5.4 mg/L
Year	:	
GLP	:	No
Test substance	:	
Method	:	
Method detail	:	
Result	:	The LC50 was reported to be > 5.4 mg/L
Remark	:	Also tested sodium propionate, dust aerosol, with same result.

Supporting data for dissocation products:
Acid: Under similar conditions as reported above for calcium propionate and sodium propionate, the LC50 for propionic acid was >4.9 mg/L. (See Appendix I: 5.1.2)

Reliability : [4] Not assignable. Only secondary literature
Reference : BASF AG, Dept. Toxicology, unpublished study 78/29, 19.12.1980. As cited in IUCLID (2000)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	500 mg/kg bw
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	The LD50 was reported as 500 mg/kg bw
Remark	:	No further information. Same result cited for propionic acid
Reliability	:	[4] Not assignable. Only secondary literature.
Reference	:	Patty Ind. Hyg. Toxicol. (1982); Smyth, H.F. et al., Am. Ind. Hyg. Assoc. J. 23:95-107 (1962); Union Carbide Datasheet. As cited in IUCLID (2000)

5.2.1 SKIN IRRITATION

Type	:	Skin irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	1973
GLP	:	No
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize skin irritation test with rabbits. (See Appendix 1: 5.2.2) **Supporting data for dissociation products:** **Acid:** Propionic acid caused mild irritation to rabbits following 4 h closed contact of the skin with a 2.5% aqueous solution, mild to moderate irritation with 25% solution, and moderate to severe irritation and corrosion at

		concentrations of 40% and above. Propionic acid ws a severe irritant to guinea pig skin. (See Appendix I: 5.2.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.2.2 EYE IRRITATION

Type	:	Eye irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Method	:	
Year	:	1973
GLP	:	
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize eye irritation test with rabbits. Propionic acid was irritating to rabbits (See Appendix 1: 5.2.2)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.4 REPEATED DOSE TOXICITY

Type	:	Repeated dose
Guideline/method	:	
Species	:	Rat
Strain	:	Wistar Han/BGA
Sex	:	Male and female
Number of animals	:	40
Route of admin.	:	Oral feed
Exposure period	:	90 days
Frequency of treatment	:	Daily
Post exposure period	:	One group for control and two highest doses over 90 and 180 days
Doses	:	0.2, 0.5, 1 and 4% (= 166, 415, 830, 3320 mg/kg bw)
Control group	:	Yes
NOAEL	:	0.2% (166 mg/kg) for males, 1% (830 mg/kg) for females
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Not clarified but presumed to be calcium propionate
Method	:	

Method detail	:	
Result	:	No abnormalities in clinical and hematological examination and organ weights. In forestomach of males, hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. In forestomach of females, hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in different regions of forestomach. Effects largely reversible during 90-day post exposure observation period. After 180 days appearance of first age-related changes in the forestomach.
Remark	:	Forty female Wistar rats fed sodium propionate at 20000 ppm (1320 mg/kg) for one year did not exhibit any hematological, clinicochemical, or urinalytic changes. There were no changes in organ weights and the body weight at the end of the study was 290 g versus 299 g in controls. [Imai, S. , S. Sekigawa, J. Morimoto, Y. Ohno, H. Yamamoto, T. Okuyama, K. Nakamor and Y. Tsubura (1981). Additive toxicity of sodium propionate and/or sorbic acid in SLC-Wistar rats for one year. J. Nara. Med. Ass. 32:715-722. Also interpreted and cited in IUCLID (2000)]. **Supporting data for dissociation products:** **Acid:** Beagles fed propionic acid for 90 days exhibited lack of appetite at the highest dose (2000 mg/kg bw) but no other clinical, hematological or clinico-chemical effects. (See Appendix I: 5.4). Propionic acid in the diet (4% or 3320 mg/kg) of rats caused enhanced incorporation of methyl-H3-thymidine in the mucosa of the forestomach after 21 and 28 days of treatment, and macroscopic and histological lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days. This may reflect the response of the forestomach epithelium to changed pH (Rodrigues, C., Lok, E., Nera, E., Iverson, F., Page, D., Karpinski, K. and Clayson, D.B., 1986. Short-term effects of various phenols and acids on the Fischer 344 male rat forestomach epithelium, Toxicology 38:103-117).
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Altman H-J and Grunow, W., „Ergeb. Neuer. Fuetterungsvers.m.Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin ,’88). As cited in IUCLID (2000)

5.5 GENETIC TOXICITY ‘IN VITRO‘

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Repair test (rec assay) and reversion assay
Species	:	*Bacillus subtilis* (rec assay); *Escherichia coli* and *Salmonella typhimurium* (reversion assay)
Strain	:	*B. subtilis*: H17 Rec^+ and M45Rec^-; *E.coli*: WP2 *hcr trp*; *S. typhimurium*: TA98, TA100, TA1535, TA 1537, TA1538
Test concentrations	:	No data specified
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. Activation system consisted of S-9 mix prepared from liver homogenate of Arochlor 1254-pretreated male rats (i.p at 500 mg/kg)
Year	:	
GLP	:	No data
Test substance	:	Calcium propionate; purity > 98%
Method	:	Rec assay using paper disk method, according to Shirasu, Y. et al., Mutat. Res. 56: 121-129. Reverse mutation assay according to Ames, B.N., Mutat. Res. 31: 347-364
Method detail	:	REC-assay (repair test): Overnight cultures of *B. subtiis* H17 Rec^+ and M45$^-$ were streaked on to a B2 auger plate and a paper disk soaked with

		0.02 ml of a solution of Ca propionate was placed on the starting part of the bacterial streaks. Plates were incubated for 1 to 2 days. The length of the inhibition zone for each streak was measured and differences of 3 mm were considered positive. Kanamycin was a positive control. Reverse mutation assay: *Eschoricia coli* W2 her and 5 *Salmonella typhurium* testers strains were used in a top-auger overlay method. Ca propionate was dissolved in DMSO and, with and without addition of S9 fraction (from AROCHLOR 1254 exposed rats) in buffer. This soluton was poured on to minimal glucose agar plate with modified Vogel-Banner E medium. Revertants were scored after two days incubation at 37^{o}C.
Result	:	Negative
Remark	:	Sodium propionate was negative in the Ames assay. (Ishidate, et al., 1984, as cited in Basler et al., 1987) **Supporting information for dissociation products:** **Acid:** Propionic acid was evaluated for genotoxic properties using the *E.coli* DNA repair assay, the SOS chromotest, the Salmonella/microsome mutagenicity test, the sister chromatid exchange test *in vitro* and the micronucleus test *in vivo*. All tests except the DNA repair assay yielded negative results. The authors concluded that this evidence supported other evidence, including studies with calcium and sodium propionate, that propionic acid was not mutagenic (Basler, A., von der Hude, W. and Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290). The authors conclude that since calcium and sodium propionate dissociate in aqueous solution and react with a proton to form the acid, results with all three test substances can be compared.
Reliability	:	[2] Reliable with restrictions. Conducted according to scientifically acceptable methods.
Reference	:	Ohta, T., M. Moriya, Y. Kaneda, K. Watanabe, T. Miyazawa, F. Sugiyama and Y. Shirasu (1980). Mutagenicity screening of feed additives in the microbial system. Mutat. Res. 77: 21-30. Also cited in IUCLID (2000)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay and dominant lethal assay
Guideline/method	:	
Species	:	Rat
Strain	:	Sprague-Dawley CD
Sex	:	male
Route of admin.	:	Oral (gastric intubation)
Exposure period	:	Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses	:	5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year	:	1973
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	Negative control (saline) and postive control used. Single dose study conducted with two rats at 5000 mg/kg bw, then repeated with ten rats at same dose.
Result	:	No increase of chromosome aberrations in bone marrow cells. In addition, no dominant lethal mutations detected.
Remark	:	No increase in chromosome abberations in the bone marrow cells of the rat were observed after dosing with sodium propionate (See Appendix I: 5.6) **Supporting data for dissociation products:**

Acid: Propionic acid was not genotoxic in the micronucleus test *in vivo*. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).

Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

Type	:	Host mediated assay
Guideline/method		
Species	:	Mouse
Strain	:	ICR
Sex	:	Male
Route of admin.	:	Oral (gastric intubation)
Exposure period	:	Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses	:	5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year	:	1973
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	Negative control (saline) and positive controls used. Ten animals at each dose level for both acute and subacute study.
Result	:	Increase in reversion frequency of *S. typhimurium* G-46 but not dose-related. No mutations in strain TA-1530 and *Saccharomyces cerevisiae* D3. A single dose was marginally recombinogenic in the acute trials using *S. cerevisiae* D3 but none of the other acute or subacute doses showed this effect.
Remark	:	
Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Mouse
Strain	:	Albino CD-1
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 17 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	1972
GLP	:	No

Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 25-30 mice were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 17 of gestation. On day 17 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the soft or skeletal tissues in treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Rabbit
Strain	:	Dutch-belted
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -18 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 29 of gestation
Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 15-25 rabbits were used. Negative controls were intubated with water, positive controls were administered 2.5 mg/kg of 6-aminonicotinamide on day 9. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,12,18 and 29 of gestation. On day 29 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, mplantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was

		examined for anatomical normality. All fetuses were examined grossly for abnormalities. Live fetuses were placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed and examined for visceral abnormalities (by dissection), then cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Hamster
Strain	:	Golden hamsters from an outbred strain (no further data)
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -10 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 14 of gestation
Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 22 golden hamsters were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,8,10, and 14 of gestation. On day 14 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not

		consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Rat
Strain	:	Albino, Wistar
Sex	:	Female
Route of admin.	:	Oral intubation
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 20 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 24 rats were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 20 of gestation. On day 20 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effect on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Chicken
Strain	:	
Sex	:	
Route of admin.	:	Injection into air cell or yolk sac of eggs

Exposure period	:	Preincubation or at 96 hours
Frequency of treatment	:	
Duration of test	:	
Doses	:	5, 10, 100 mg/kg of egg
Control group	:	Yes, concurrent vehicle
NOAEL maternal tox.	:	
NOAEL teratogen.	:	100 mg/kg
Other	:	High mortality rates at doses of 5 and 10 mg/kg
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Calcium propionate
Method	:	
Method detail	:	
Result	:	Not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg preincubation or at 96 h via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered preincubation via the yolk caused a high mortality rate.
Remark	:	
Reliability	:	[4] Not assignable. Only secondary reference.
Reference	:	Mississippi State University, 1973. Investigation of the toxic effects of GRAS substances to the developing chicken embryo: calcium propionate. As cited in FASEB (1979)

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

6.0 OTHER INFORMATION

6.1 CARCINOGENICITY

Supporting information for dissociation products:

Acid: Pre-neoplastic/pre-cancerous changes in rats fed 4% (2640 mg/kg) propionic acid were reported by Griem (1985). Hyperplasia, hyperplastic ulcers, papillomas and proliferation of the basal cells in the mucuosa of the forestomach were observed. Over the lifetime exposure, the high dose (4% propionic acid) resulted in 19/20 rats with dysplasia of glandular stomach mucosa while this effect was seen in 10/20 rats at the low dose (0.4%) and 5/20 control rats. However, Basler et al. (1987) concluded that propionic acid is not mutagenic and that genotoxic events are unlikely to be involved in the generation of these forestomach lesions. (See Appendix I: 5.7; also Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).

6.2 EXEMPTION FROM TOLERANCE:

Supporting Decision by the Environmental Protection Agency, Office of Pesticide Programs to grant an Exemption from Tolerence:
In the Federal Register , August 4, 2004 [(Volume 69, Number 149), Rules and Regulations, pages 47022-47025] a Final Rule was announced. This regulation establishes an exemption from the requirement for tolerance for residues of propanoic (propionic) acid and its calcium and sodium salts on alll raw agricultural commodities, ...and reorganizes current tolerance exemptions. The action was initiated by a company interested in only three crops sugar beets, potatoes and sweet potatoes under the Food , Drug, and Cosmetic Act (FFDCA), as ammended by the Food Quality Protection Act of 1996. The EPA reviewed the existing data relative to human health and published a proposed rule persuant to section 408 of FFDCA. The expanded rule presented in this Federal Register notice establishes a broad exemption for tolerance for any residues of propanoic (or propionic) acid and the respective calcium and sodium salts on all crops when the chemicl is used as a fungicide or as an inert inredient in pesticides.